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Alteration of Cell Surface Glyconjugates in Leukemia and Breast Cancer Cells

A wide variety of sugar chains modify proteins that are found on the surface of cells. The size and type of sugar chains found on cell surface proteins change during development and during the formation of tumors. Generally, these sugar chains will become longer and more complex, and frequently, there will be a higher proportion of a charged sugar called sialic acid. Specific sugar chains have been demonstrated to influence interactions between cells. Long chains of sialic acid (polysialic acid chains) are thought to decrease the interaction of cells and allow their increased migration. This situation would be advantageous during development of organ systems and also would lead to detachment of tumor cells and their migration into surrounding tissue to form new tumors. The long polysialic acid sugar chains observed during development and in cancer have always been associated with a protein called neural cell adhesion molecule or NCAM. These specific sugar chains have always been observed on NCAM, located exclusively on the cell surface, where they could exert their effects on cell-cell interactions. Our laboratory has found that two cancer cell lines, a human breast cancer line and a rat basophillic leukemia cell line, which have a different pattern polysialic acid chain expression than most cancer cells (such as a human small cell lung cancer cell line). In these two cancer cells, the polysialic acid chains are found only in a compartment inside the cell. In addition, we do not see NCAM on the cell surface of these two cancer cell lines. It is possible that the polysialic acid chains are added too early in the lifetime of the proteins and this leads to the retention of cell surface proteins (such as NCAM) inside the cell. The goal of our research is to identify the proteins which are modified by polysialic acid chains and retained inside the human breast cancer cell line and the basophillic leukemia cell line, and determine whether these sugar chains are added prematurely to these proteins leading to their abnormal location inside these cells. It is possible that the pattern (location) of expression of polysialic acid chains determines the interactions cancer cells have with their environment and other cells. This research project should give us tools to predict how other cancer cells interact with surrounding tissues and their environment based on the location of polysialic acid chains in these cells.

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Retinoic Acid – Regulated Genes and Differentiation

Vitamin A and its chemical relatives, the retinoids, are important regulators of cell growth and differentiation in a broad array of tissues. Indeed, vitamin A deficiency is clearly associated with premalignant changes and neoplastic development. Retinoic acid (RA) has also been found to reverse the malignancy of several tumor cell lines. More importantly RA treatment can repress acute promyelocytic leukemia (APML), oral cancer and skin cancer. In tumor cell lines, and presumably *in vivo*, RA exerts its effect by activating a cascade of gene expression which culminates in terminal differentiation and the irreversible loss of the neoplastic phenotype. APML repression is particularly interesting because APML is associated with mutation of a gene required for RA-regulated gene expression. Induction and repression of growth factors are central to this process. One embryonal carcinoma cell line, F9, has been very useful for biochemical and molecular studies of differentiation. RA causes the malignant F9 embryonal carcinoma cells to change into benign cells. I found that RA interacts with 2 growth factors, BMP-2 and -4, to alter the differentiation of F9 cells. This work suggested that these BMPs are involved in RA-induced differentiation. I will analyze these interactions, in order to understand how RA induces malignant cells to differentiate into nonproliferating, benign cells. Elucidation of how the BMPs and RA regulate differentiation *in vitro* will contribute to an understanding of how retinoids regulate normal and neoplastic differentiation. More specifically, understanding how retinoids induce differentiation should lead to improved cancer differentiation therapies, like those used to treat APML and oral cancer.